ABSTRACT
Nicotinamide (vitamin B₃) has a range of photoprotective effects in vitro and in vivo; it enhances DNA repair, reduces UV radiation-induced suppression of skin immune responses, modulates inflammatory cytokine production and skin barrier function and restores cellular energy levels after UV exposure. Pharmacological doses of nicotinamide have been shown to reduce actinic keratoses and non-melanoma skin cancer incidence in high-risk individuals, making this a nontoxic and accessible option for skin cancer chemoprevention in this population.

Key words: basal cell carcinoma, melanoma, niacinamide, squamous cell carcinoma, vitamin B₃.

INTRODUCTION
Despite frequent public campaigns and health practitioner advice highlighting the need for sun protection, skin cancer incidence continues to increase in our ageing population. Even individuals at highest risk of skin cancer tend to use sunscreen suboptimally. While there is considerable scope for improving the uptake of sun protection behaviour and sunscreens, additional systemic chemoprevention is often needed for those at extreme skin cancer risk.

A wide range of agents has been assessed for photoprotective efficacy. Botanical agents such as the carotenoid antioxidant lycopene can reduce sensitivity to UV-induced erythema. Leucotomos extract and flavonoids also reduce UV-induced immune suppression, which plays a key promotional role in skin carcinogenesis. As yet there is no evidence of these agents’ ability to reduce skin cancer incidence in humans. Initial work on the chemopreventive effects of nonsteroidal anti-inflammatory drugs (NSAID) such as celecoxib suggests that these agents may help to reduce the incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), but as yet confirmatory phase 3 studies are lacking. NSAID also carry potential gastrointestinal, renal and cardiovascular side-effects that limit their tolerability in many patients.

Oral retinoids such as acitretin can help to reduce non-melanoma skin cancer incidence and have been regarded as first-line systemic agents for skin cancer chemoprevention in patients at extreme risk. Retinoids carry a range of potential side-effects including liver function and lipid abnormalities, dry skin and eyes and teratogenicity, which limit their tolerability and their suitability for many patients. As yet, no systemic agents have been shown to be effective for the chemoprevention of melanoma.

Nicotinamide (niacinamide) and nicotinic acid (niacin) are forms of vitamin B₃. Both have photoprotective effects in animal models. In UV-irradiated mice, topical nicotinamide reduced skin cancer incidence from 75% to 43% (P = 0.016), while feed supplementation with 0.1, 0.5 or 1.0% niacin dose-dependently reduced skin cancer incidence from 68% (control) to 60, 48 (P = 0.038) and 28% (P = 0.026), respectively. Nicotinic acid is an effective lipid lowering agent, but has pronounced vasodilatory side-effects such as flushing, headache, hypotension and itch, which are not seen with nicotinamide. High-dose

Abbreviations:

<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>8oxoG</td>
<td>8-oxo-7,8-dihydro-2′-deoxyguanosine</td>
</tr>
<tr>
<td>AK</td>
<td>actinic keratosis</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>BCC</td>
<td>basal cell carcinoma</td>
</tr>
<tr>
<td>CPD</td>
<td>cyclobutane pyrimidine dimer</td>
</tr>
<tr>
<td>NAD</td>
<td>nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>ONTRAC</td>
<td>oral nicotinamide to reduce actinic cancer</td>
</tr>
<tr>
<td>PARP-1</td>
<td>poly-ADP-ribose polymerase 1</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
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<tr>
<td>SCC</td>
<td>squamous cell carcinoma</td>
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Nicotinamide has been used in clinical practice for many years for the treatment of autoimmune blistering disorders such as bullous pemphigoid. Nicotinamide is widely available commercially in many countries, including Australia, as 500 mg tablets and also at doses of 14—50 mg in a range of multivitamin preparations.

NICOTINAMIDE REPLENISHES CELLULAR ENERGY

As a precursor of nicotinamide adenine dinucleotide (NAD\(^+\)), an essential cofactor in adenosine triphosphate (ATP) production, nicotinamide plays a central role in cellular energy metabolism. Hence, nicotinamide deficiency (pellagra) is characterised by dysfunction in organs with high-energy requirements such as the brain, gut and skin. The ‘four D’s’ of pellagra — dementia, diarrhoea, photodistributed dermatitis and death — are prevented by a recommended daily nicotinamide intake of 15—20 mg, readily obtainable from dietary sources such as meat, fish, eggs, milk, legumes, cereals and yeast.

Cutaneous energy requirements are further increased after UV radiation exposure, in order to fuel the highly energy-intensive process of DNA repair. UV radiation not only damages DNA but also reduces cellular energy availability by blocking glycolysis and depleting cellular ATP. Both cellular NAD\(^+\) pools and DNA repair efficiency are known to be relatively reduced with age. In addition, UV exposure activates the nuclear poly-ADP-ribose polymerase (PARP), which has key roles in DNA repair. NAD\(^+\) is the sole substrate of PARP, such that excessive PARP activation (e.g., following UV exposure) depletes the cellular NAD\(^+\) (energy) pool. Even in unirradiated skin, NAD\(^+\) depletion and increased PARP activity can be observed with increasing age and is more pronounced in men than in women.

Nicotinamide helps to prevent this UV-induced energy crisis, unblocking glycolysis and restoring ATP levels in human keratinocytes exposed to solar-simulated UV radiation. Nicotinamide is also a PARP inhibitor. We have shown that 50 μmol/L nicotinamide can inhibit PARP-1 activity by 66%; 95% PARP-1 inhibition is seen with nicotinamide at 500 μmol/L. The concentration of nicotinamide included in commercially available cell culture media to enable normal viability is ~55 μmol/L, and extremely high doses of nicotinamide (6 g) are reported to produce median plasma levels of ~1.1 mmol/L. Hence 50 μmol/L represents a physiologically readily achievable level.

NICOTINAMIDE ENHANCES DNA REPAIR

Even low doses of UV radiation, equivalent to one-third of a minimal erythema dose (sunburn threshold), can cause measurable DNA damage in the skin. Cyclobutane pyrimidine dimers (CPD) and oxidative DNA damage (8-oxo-7,8-dihydro-2’-deoxyguanosine [8oxoG]) can result from exposure to both UVB (290—320 nm) and UVA (320—400 nm), although UVB predominantly causes CPD while UVA is more efficient at producing oxidative photodam-ages. Normal cellular metabolism, with resultant reactive oxygen species (ROS) formation, also causes basal levels of 8oxoG in unirradiated skin. Relatively higher levels of basal 8oxoG are seen in melanocytes compared to keratinocytes, probably reflecting the less efficient DNA repair observed in melanocytes.

While most DNA damage is repaired with maintenance of genomic stability, inefficient and incorrect repair can result in mutations. DNA repair efficiency diminishes with individuals’ age, and those with a history of melanoma or nonmelanoma skin cancer have less efficient DNA repair than age-matched controls.

Nicotinamide reduces levels of CPD and 8oxoG in UV-irradiated human keratinocytes, melanocytes and ex vivo irradiated skin, and reduces basal levels of 8oxoG in unirradiated melanocytes. It does not prevent DNA damage by UV radiation (levels immediately after UV are equivalent in nicotinamide-treated and untreated cells), and it does not measurably increase the in vivo sunburn threshold in humans. Hence, nicotinamide does not act as a sunscreen. At physiologically achievable concentrations in human keratinocytes, nicotinamide did not alter rates of basal or UV-induced levels of ROS hydrogen peroxide or superoxide, and hence does not reduce 8oxoG via direct antioxidant effects. Human fibroblasts cultured with nicotinamide have, however, shown reduced ROS and oxidative damage, suggesting that nicotinamide may have indirect, downstream antioxidant activity. In these studies, nicotinamide increased fibroblast replicative lifespan, associated with a reduced rate of telomere shortening but with no detectable effects on telomerase activity.

Rather than preventing UV-induced DNA damage, nicotinamide enhances the rate of DNA repair, confirmed in human keratinocytes and melanocytes by unscheduled DNA synthesis assays. Rates of scheduled DNA synthesis (programmed cell division) were unaffected by nicotinamide, but DNA synthesis in response to DNA damage was significantly increased. There was no detectable effect of nicotinamide on levels of the 8oxoG repair enzyme HOGG1, suggesting that the enhancement of DNA repair is largely mediated by nicotinamide’s role in boosting cellular energy. Nicotinamide also upregulates DNA repair in UV-irradiated lymphocytes. Older mice display lower rates of unscheduled DNA synthesis than young mice; nicotinamide enhanced DNA repair in all animals but was twice as effective in older mice.

At physiologically achievable concentrations, nicotinamide can also inhibit sirtuins. These NAD-dependent enzymes play central roles in cellular metabolism and energy management, ageing and stress responses. Sir-tuins appear to have proinflammatory effects, which can play a promotional role in carcinogenesis; they are also regulators of cancer cell metabolism, and may increase tumour survival. Nicotinamide inhibition of sirtuins, with downstream effects on inflammation and cancer metabolism, is another possible mechanism of its chemopreventive activity.
NICOTINAMIDE REDUCES THE IMMUNE SUPPRESSIVE EFFECTS OF ULTRAVIOLET RADIATION

Immunosuppression promotes cutaneous carcinogenesis. Unrepaired DNA damage is a key trigger for the suppressive effects of UV radiation on skin immunity. Even low-dose suberythema UV radiation can significantly impair skin immune responses. This immune suppression is reversed by the addition of DNA repair enzymes such as T4N5 liposomes.

Murine studies have shown that nicotinamide prevents the immune suppressive effects of UV radiation when given topically or orally. In healthy, Mantoux-positive volunteers, topical or oral nicotinamide reduced UV-induced suppression of delayed-type hypersensitivity responses to tuberculin. Nicotinamide was effective when applied either before or immediately after UV exposure, again indicating that it is not acting as a sunscreen. Nicotinamide confers broad-spectrum immune protection, offering similar protection against both short wave narrowband UVB (310 nm) and long wave UVA (370 nm).

Oral nicotinamide at doses of 500 mg once daily to 500 mg thrice daily for 7 days was also effective in reducing UV immunosuppression in Mantoux-positive volunteers in placebo-controlled crossover studies. Notably, nicotinamide did not enhance baseline cutaneous immunity (Mantoux intensity) at unirradiated sites but rather helped to normalise immune responsiveness at UV-irradiated sites. Individuals with a past history of melanoma or nonmelanoma skin cancer are intrinsically more susceptible to UV-immunosuppression, and hence these individuals might obtain relatively greater immune protective benefit from nicotinamide than individuals with more robust skin immunity.

INFLAMMATION AND SKIN BARRIER FUNCTION

Inflammation is a known driver of carcinogenesis. Disruption of skin barrier function, and the inflammation that follows, can promote excessive epidermal proliferation and skin cancer induction in animal models. Nicotinamide modulates a range of inflammatory cytokines and has been used in the treatment of autoimmune and inflammatory dermatoses including bullous pemphigoid, rosacea and acne. Maternal serum levels of nicotinamide are inversely correlated with atopic dermatitis incidence in infants. Previous studies have suggested that nicotinamide may improve skin barrier function, possibly by its effects on aquaporins, which modulate cellular hydration. We found that oral nicotinamide (500 mg twice daily) significantly reduced transepidermal water loss in 292 mainly elderly participants with multiple previous skin cancers.

NICOTINAMIDE REDUCES ACTINIC KERATOSES

In order to assess whether nicotinamide’s photoprotective effects on the skin extend to skin cancer chemoprevention, we used premalignant actinic keratoses (AK) as a surrogate measure of chemoprevention efficacy in a series of phase 2 studies. Twice daily application of 1% nicotinamide lotion significantly reduced numbers of AK on the face, scalp and forearms of 50 sun-damaged patients by 22% compared to a 10% reduction in patients receiving base lotion in this 6-month, double-blind study ($P = 0.04$).

Oral nicotinamide at doses of 500 mg twice daily and 500 mg once daily was next evaluated in two placebo-controlled phase 2 trials in patients with an average of more than 50 AK at baseline. Within 4 months we observed significant relative reductions in AK of 55 and 29% with twice daily and once daily nicotinamide dosing, respectively. The effect of nicotinamide on AK counts was independent of baseline AK counts, with similar reductions in the worst-affected and least-affected patients. A total of 74 patients was followed up in these phase 2 studies. Comparison of nonmelanoma skin cancer rates (BCC + squamous cell carcinoma [SCC]) in those receiving nicotinamide compared to those in the placebo arms showed a significant reduction within the 4-month study period. While 11 participants in the placebo groups developed a total of 20 new skin cancers (12 BCC and eight SCC) within 4 months, only four new skin cancers (two BCC and two SCC) developed in two participants in the nicotinamide groups (relative rate =0.24, $P = 0.01$, Poisson regression model adjusting for study and number of previous skin cancers). Skin cancer incidence was not, however, a pre-specified end-point of these AK studies, and phase 3 evidence was required.

ORAL NICOTINAMIDE TO REDUCE ACTINIC CANCER: THE ONTRAC STUDY

The phase 5 double-blind randomised controlled ONTRAC study was designed to assess the chemopreventive effectiveness and safety of nicotinamide in high-risk patients.

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site, BCC and SCC counts during the intervention period and skin cancer incidence 6 months’ post-intervention.

The primary end-point of the ONTRAC study was number of new, histologically confirmed nonmelanoma skin cancers to 12 months. After adjustment for study site and number of histologically confirmed skin cancers in the past 5 years, patients receiving nicotinamide showed a 25% relative rate reduction in new nonmelanoma skin cancers (BCC and SCC) compared to placebo ($P = 0.02$); the unadjusted relative rate reduction was 27% ($P = 0.02$). There were similar magnitudes of reduction for both BCC (relative rate reduction 20%, $P = 0.12$) and SCC (relative rate reduction 50%, $P = 0.05$). AK counts followed the same trend; significant relative reductions in AK counts were observed throughout the intervention period at 5, 6, 9 and 12 months. Nicotinamide’s effectiveness in reducing AK counts appeared to plateau after the 9-month visit.2

Relative reductions in new skin cancers were noted as early as 5 months into the intervention period, but the chemopreventive effects of nicotinamide were rapidly lost post-intervention; skin cancer incidence in the 6-months post-intervention was identical in the placebo and nicotinamide arms.2 Hence, nicotinamide most likely acts to slow the progression of already initiated cancer cells.

BCC subtypes and SCC grades
Nicotinamide appeared to be relatively more effective in reducing relative rates of superficial BCC compared to other BCC subtypes. Although numbers were small, there was no reduction in numbers of the more aggressive BCC subtypes (micronodular, infiltrating or morphoeic).2 All lesions reported as having these BCC subtypes were independently reviewed by a single blinded tissue pathologist to ensure consistency of reporting across both study arms. Similarly, all squamous lesions biopsied or excised were also independently reviewed by a single blinded tissue pathologist. We found no difference in nicotinamide’s effectiveness in reducing SCC in situ versus well-differentiated and versus moderately-differentiated SCC.2

Factors influencing chemopreventive effectiveness
A number of pre-specified factors were examined in the ONTRAC study to determine predictors of chemopreventive efficacy. We found no influence of gender, age, smoking status or concurrent use of NSAID or statins; the only factor that appeared to influence efficacy was previous number of nonmelanoma skin cancers. Patients with the highest numbers of skin cancers in the previous five years (>6) seemed to respond more effectively to the chemopreventive effects of nicotinamide than patients with five cancers or fewer in the previous 5 years.2 Individuals with previous skin cancers have greater susceptibility to UV immune suppression39 and younger patients with previous BCC were found to have reduced DNA repair capacity compared to age matched controls, although DNA repair capacity in cases and controls gradually equalised with age.42 It may be that nicotinamide is better able to normalise the anti-cancer defences of higher risk individuals. It may also be that longer timeframes are needed to observe significant chemoprevention in patients who would normally develop only one or two new cancers per year. With known reductions in cellular NAD and DNA repair capacity with age, especially in men, we may have expected to observe greater chemopreventive efficacy of nicotinamide in older participants and in men; however, this was not the case.2

Optimum nicotinamide dosing
The ONTRAC study used nicotinamide 500 mg twice daily, chosen because this dose resulted in a slightly greater and more rapid reduction in AK compared with 500 mg once daily in our phase 2 AK studies.46 Our earlier UV immunosuppression studies, however, found comparable protection afforded by 500 mg once daily and thrice daily, although these were studies in healthy Mantoux-positive participants with intervention for only 7 days.30 The optimum long-term nicotinamide dose for skin cancer chemoprevention is not known. It may be that 500 mg or even 250 mg daily provides similar efficacy as the 1 g daily dose used in ONTRAC. There was no correlation between participants’ bodyweight and the chemopreventive effectiveness of a 1 g daily dose (i.e., no detectable reduction in efficacy in patients with a higher bodyweight), implying that chemopreventive efficacy may have been saturated at 500 mg twice daily and that lower doses may also be effective. As yet, there are no data comparing the efficacy or tolerability of a single 1 g daily dose to a divided dose of 500 mg twice daily, as was used and found to be well-tolerated in the ONTRAC study.2 Blood NAD levels following a 500 mg nicotinamide dose in healthy volunteers were previously noted to return to baseline within 90 min of dosing29 (suggesting that divided dosing may be more appropriate) although it may be that a steady state for NAD levels in the skin can be achieved with repeated dosing.

Safety and tolerability
Unlike nicotinic acid, nicotinamide does not cause vasodilatory side-effects48 and has been well tolerated at high doses (1.5—5 g daily) for a range of clinical and research indications including for inflammatory skin diseases,14 as a radiosensitiser22 and in diabetes prevention studies in children and adults.49 Nicotinamide has an established safety profile even at high doses,15 although a reversible elevation of liver enzymes and nausea have been reported in some patients at much higher daily doses (8 g daily).50 The ONTRAC study cohort included patients ranging in age from 50 to 91 years (mean 66 years), many with multiple comorbidities and receiving numerous concurrent medications. Almost a quarter of our 586 patients experienced at least one hospitalisation within the 12-month intervention.2 The 86 serious adverse event reports

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(some patients experienced multiple concurrent serious adverse events), were evenly distributed across the placebo and nicotinamide arms, with no notable between-group differences in adverse events nor in blood pressure or bodyweight (measured 3 monthly for 12 months), full blood count, renal function or hepatic function (measured at baseline and 12 months).2

Nicotinamide inhibits phosphate co-transport in the gut and renal proximal tubule and has been used as a phosphate-lowering agent in haemodialysis patients, at doses of 1—2 g daily.51 Lenglet and colleagues reported four cases of thrombocytopaenia (to <70 000/mm3) in 49 haemodialysis patients taking an average of 1.5 g nicotinamide daily, although there was no overall change in mean platelet count from baseline in patients taking nicotinamide.51 All cases of thrombocytopaenia resolved after the withdrawal of nicotinamide. This study also found an increased incidence of nausea and diarrhoea with nicotinamide,51 which we did not see in the ONTRAC study,2 which excluded patients with renal failure. Nicotinamide is renally excreted and hence may present a different side-effect profile in renal impairment.

Nicotinamide has few established drug interactions. There is a possible interaction with carbamazepine,52 and so nicotinamide may be best avoided in patients taking this medication. The effect of oral nicotinamide at pharmacological doses on the absorption and metabolism of oral contraceptives is also unknown.

NICOTINAMIDE FOR SKIN CANCER CHEMOPREVENTION AFTER TRANSPLANT

The incidence of nonmelanoma skin cancer is increased 50—80-fold in chronically immune-suppressed transplant recipients,53 and melanoma is at least twice as frequent in transplant recipients.54 Small phase 2 studies suggest that nicotinamide may also have chemoprotective effects in immune-suppressed transplant recipients. Drago and colleagues randomised 24 renal transplant recipients to receive placebo or nicotinamide 250 mg thrice daily for 6 months and found reductions in AK without detectable effects on the blood levels of immune-suppressed patients.55 We randomised 22 renal transplant recipients to placebo or nicotinamide 500 mg twice daily and found nonsignificant trends to reduction in new skin cancers and AK over the 6-month intervention period in this small cohort.56 A mean of 4.2 new skin cancers (BCC + SCC) developed in patients taking placebo (95% CI 2.2—7.8, 45 cancers in total) compared to a mean of 2.7 new cancers in the group taking nicotinamide (95% CI 1.4—5.3; 50 cancers in total). AK counts were 16% lower with nicotinamide at 6 months ($P = 0.15$).

Blood and urine samples were taken at baseline and 2 and 4 weeks and at 2, 4 and 6 months. There was no significant increase in adverse effects nor significant change in blood or urine parameters or blood pressure, but this was a small pilot study only and larger studies are needed to confirm nicotinamide’s safety and efficacy in this medically complex population.

NICOTINAMIDE FOR MELANOMA CHEMOPREVENTION

DNA photodamage and UV-induced immune suppression are central in the development of melanoma as well as nonmelanoma skin cancer.55,57 Nicotinamide’s effects on DNA repair and immune protection suggest that it may be useful in melanoma as well as nonmelanoma skin cancer chemoprevention. We found similar effects of nicotinamide on the repair of CPD and oxidative DNA damage after UV in human keratinocytes and phaeomelanin and eumelanin-producing human melanocytes.23,28 In these studies we found higher basal levels of oxidative DNA damage in melanocytes than in keratinocytes, consistent with the reduced DNA repair efficacy in melanocytes.23 Nicotinamide also reduced levels of basal oxidative DNA damage in unirradiated melanocytes.28

The ONTRAC study comprised participants at high risk of developing nonmelanoma skin cancer and did not specifically select for melanoma risk. Hence only six in situ and four invasive melanomas developed during the 12-month study period (evenly distributed between the nicotinamide and placebo arms).2 Hence, larger phase 3 studies of nicotinamide for melanoma chemoprevention are now indicated in high-risk patients in order to both to determine efficacy but also to cross-check safety in this group.

ARSENICAL CARCINOGENESIS

Populations chronically exposed to arsenic in drinking and irrigation water develop arsenical keratoses and increased rates of SCC and BCC. Large populations are affected across West Bengal and Bangladesh (150 million) and China (20 million), where ground water accessed by tube wells is heavily contaminated with arsenic.58 Arsenic and UV radiation act as co-carcinogens in animal models;59 arsenic is thought to both damage DNA and also to impair DNA repair. We found that nicotinamide significantly enhanced rates of DNA repair in arsenic-exposed, UV-irradiated keratinocytes and ev vivo human skin.60 Hence, nicotinamide may also have potential for the inexpensive chemoprevention of chemical carcinogenesis in arsenic-affected populations.

NICOTINAMIDE CHEMOPREVENTION IN THE CLINIC

Phase 3 evidence from the ONTRAC study showed that oral nicotinamide can reduce nonmelanoma skin cancer incidence by a quarter in high-risk, immune-competent individuals. There were similar reductions in both BCC and SCC, and consistent reductions in premalignant AK. We found greater chemopreventive efficacy in the patients at highest risk, which may be due to the greater susceptibility of these extreme-risk individuals to both UV-induced immunosuppression, cellular energy deficit and reduced DNA repair capacity.61 As yet, there is no evidence of nicotinamide’s chemopreventive

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effectiveness in lower risk populations, and so pharmacological dose nicotinamide is best reserved for suitable patients with multiple previous nonmelanoma skin cancers. It is important to ensure that patients take nicotinamide and avoid nicotinic acid, and to emphasise the need for ongoing regular sunscreen use and skin surveillance.

At this time the role of nicotinamide in melanoma chemoprevention, in the management of transplant recipients and in individuals with skin cancer syndromes such as Gorlin syndrome or xeroderma pigmentosum is unclear, and nicotinamide is best offered to these patients only in the context of clinical trials. For all high-risk patients, longer term follow-up studies are now needed to determine whether nicotinamide’s effectiveness wanes or improves with time, and to determine the longer term tolerability profile in this high-risk, cancer-prone population. Animal studies have shown reduced rates of internal malignancies and leukaemias with very high-dose nicotinamide (reviewed in20), but its effects on these cancers in humans are as yet unknown.

CONCLUSION

Nicotinamide at pharmacological doses has a long history of clinical use. It is inexpensive, widely available commercially and has an excellent safety profile. Phase 3 evidence of its chemopreventive efficacy against nonmelanoma skin cancers in high-risk patients means that it is now becoming part of the routine management of this group. Its use in the broader lower risk population and in those after transplant and at high risk of melanoma, is now worth exploring in the context of clinical trials.

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